Applicants note that the Training Materials for the Revised Interim Written Description Guidelines provide examples of claims similar to those in the instant application. In particular, the Training Materials described a claim directed to a genus of proteins that comprise a specific amino acid sequence. In the example, one member of the genus (SEQ ID NO: 3) is described by a complete amino acid structure. Regarding the exemplary claim, the Training Materials stated: "There is relatively little variation among the species within the genus because each member of the genus shares SEQ ID NO: 3 as a necessary common feature. The single disclosed example is representative of the claimed genus because taken in view of the general knowledge in the art, the disclosure is sufficient to show that one of skill in the art would conclude that applicant was in possession of the claimed genus." Training Materials, Example 13, p.51.

The same principles apply to the instantly claimed invention. Claim 1 recites, in part, "An isolated MAGE-A12 HLA class I-binding peptide comprising the amino acid sequence of SEQ ID NO:6...." This portion of the claim is completely analogous to claim 1 of Example 13. Accordingly, the rejection of the claims "because it does not distinguish the claimed genus from others, except by the property of containing a portion of SEQ ID NO:2, 4, 5 or 6" is not in agreement with the written description examination guidelines and should be withdrawn.

Applicants have amended the portion of the claims that recites variants, to specifically limit the variants to sequences having one amino acid difference from the recited sequence. Applicants believe that the claims amended to recite a single amino acid variation from the recited sequences are adequately described in the specification. In particular, the sequences do not have extensive variability, with only one amino acid addition, substitution or deletion permitted. One of ordinary skill in the art would know that the Applicants had possession of this limited genus, in which each member of the genus shares the recited sequences as a necessary common feature.

The Examiner has alleged that the specification does not define "any structural features commonly possessed by members of the genus that distinguish them from others, other than that they comprise portions of SEQ ID NO:2, 4, 5 or 6." Office Action, page 7. According to the written description guidelines and the case law, however, this is sufficient to provide an adequate written description. The court in Regents of the University of California v. Eli Lilly stated that a genus must be described by a precise definition, "such as by structure, formula, chemical name or physical properties." Regents of the University of California v. Eli Lilly 119 F.3d 1559, 43

USPQ 2d 1398 (Fed. Cir. 1997). Applicants have done this by providing the specific structures of the claimed peptides, permitting one amino acid substitution. One of ordinary skill in the art can readily envision this genus based on the common structural properties set forth in Applicants' specification.

Moreover, one of ordinary skill in the art can readily identify whether a particular sequence is part of the claimed genus by performing a simple comparison of the particular sequence to the claimed sequences. Thus, because Applicants have provided an adequate written description of the claimed invention, one of ordinary skill in the art will be certain if a particular sequence is, or is not, part of the claimed genus.

Therefore, Applicants respectfully request that the rejections of the claims as not adequately described be withdrawn.

The Examiner rejected claims 1-4, 7, 8, 42 and 43 as not enabled by the specification. Applicants have amended the claims and in view of the amendments respectfully request that the enablement rejection be withdrawn.

The factors enunciated in In re Wands provide the framework for an analysis of the enablement of a claimed invention. In re Wands 858 F.2d 731, 737, 740, 8 USPQ2d 1400, 1404, 1407 (Fed. Cir. 1988). It appears that only two of eight Wands factors were considered by the Examiner. Applicants maintain that full consideration of each and all of the Wands factors, in view of the state of the art at the time of filing, leads one to the conclusion that practicing the invention as claimed would not require undue experimentation.

The Examiner considered the amount of guidance provided and the quantity of experimentation. Applicants do not agree with the Examiner's assertion that no guidance was provided. Applicants' specification provided ample guidance to one of ordinary skill in the art at the time of filing (in 2000) how to make and use the claimed peptides. For example, on pages 13-15, Applicants provided guidance for the preparation and testing of variant peptides. Example 1 provided further guidance, including specific experimental procedures used in the testing of peptide function. Thus, Applicants assert that the guidance factor is not, by itself, a sufficient reason to find undue experimentation.

Similarly, the quantity of experimentation is not sufficient to support a finding of nonenablement. The Examiner merely states that the experimentation would be "extended"

because of the alleged lack of guidance. Office Action at page 9. First, as noted above, sufficient guidance was provided to one of ordinary skill in the art for making and testing peptides including fragments and variants, which are tested by the same methods. Second, the Examiner's statement regarding the quantity of experimentation was not supported by any evidence. Office Action, page 9. The recitation of the difficulties of reconciling protein sequence and tertiary structure does not provide evidence that the quantity of experimentation would have been excessive for one of ordinary skill in the art, because the tertiary structure need not be determined in order to examine functional activity.

The Examiner did not consider the remaining *Wands* factors: 1) working examples, 2) predictability of the art, 3) breadth of the claims, 4) the nature of the invention, 5) the state of the prior art, and 6) the level of one of ordinary skill in the art. Applicants submit that consideration of these factors weighs in favor of a finding of enablement for the claimed invention.

First, Applicants provided working examples for the testing of HLA class I binding function of peptides. Second, the identification of HLA class I binding peptide molecules is not unpredictable, given that Applicants have provided the amino acid sequence of the relevant segment of the MAGE-A12 protein that was shown to be a HLA class I binding peptide. Fragments and variants can be made readily, with little effort. As noted above, the guidance provided for testing the peptides is sufficient to permit one of ordinary skill in the art to test for functional activity of any fragments or variants of the recited sequences. Third, neither the scope of the claims nor the nature of the invention is overly broad, because there is a limitation on the sequence of the claimed peptide molecules.

As in the Wands case, because of the "high level of skill in the art at the time the application was filed," and because "all of the methods needed to practice the invention were known," the claimed invention is enabled by the specification. Wands at 740, 8 USPQ2d at 1406. Applicants maintain that the same conclusions with respect to the state of the art and the level of skill in the art are true in the instant case, both of which were advanced at the time of filing, and therefore must weigh heavily in favor of a finding that undue experimentation is not required to practice the claimed invention. Accordingly, Applicants respectfully request that the rejection of the claims as not enabled by the specification be withdrawn.

Rejection Under 35 U.S.C. 112, Second Paragraph

The Examiner rejected claims 1-3, 7, 42 and 43 as being indefinite.

Applicants have amended claim 1 to recite the singular term "molecule" as requested by the Examiner.

Applicants respectfully traverse the rejection with respect to the alleged indefiniteness of claims 2 and 3. Applicants maintain that the plural terms "fragments" and "variants" are not indefinite because these terms are part of a Markush group. The claims recite that the claimed peptide has a sequence selected from the sequences in the Markush group, which may include multiple fragments and multiple variants. Accordingly, Applicants respectfully request that the Examiner reconsider the rejection of claim 2 and 3.

In view of the claims amendments and arguments presented above, Applicants respectfully request that the rejection of claims 1-3, 7, 42 and 43 as indefinite be withdrawn.

Rejection Under 35 U.S.C. 103(a)

The Examiner rejected claims 1-4, 7, 8, 42 and 43 as unpatentable over Accession No. I54519 in view of US 5,846,827, US 5,662,907 and Rammensee et al, and in view of admissions in the specification. Applicants respectfully traverse the rejection.

First, the Examiner did not perform any analysis at all regarding the level of skill in the art. Consequently one of the factual inquiries required for a determination of obviousness has not been addressed by the Examiner, and therefore the conclusion of unpatentability is not fully supported. Graham v. John Deere Co., 383 US 1, 17, 148 USPQ 459, 467 (1966).

Second, the Examiner did not demonstrate that the combination of the prior art has all of the elements of the claimed invention.

Accession No. I54519 does set forth the complete MAGE-A12 amino acid sequence, but does not teach or suggest that the specific segment identified by Applicants as a HLA class I binding molecule has that property (or any other specific property).

US 5,846,827 teaches that potential epitopes of target proteins can be identified by scanning the amino acid sequence of the target protein for certain sequence motifs, and that

motifs used for sequence scanning are specific for different HLA class I alleles. US 5,846,827 does not teach or suggest that the MAGE-A12 protein has or is likely to have HLA class I binding peptides within its sequence.

US 5,662,907 describes potential HLA-A1 epitopes in MAGE-2 and MAGE-3 proteins. This patent also describes the variability in HLA binding of the peptides identified by computer epitope searches (see Example, column 18 and Table 2); most of the identified peptides do not bind with high affinity to HLA class I. In addition, only potential HLA-A1 epitopes were identified. Further, only MAGE-1, -2 and -3 proteins were screened for HLA binding peptides. MAGE-A12 was not examined or even suggested.

Rammensee does not supply the elements missing from the other references.

Accordingly, the prior art does not contain all of the elements of the claimed invention, and therefore, the Examiner has not met the burden of making a *prima facie* case of obviousness based on the cited prior art.

The Examiner has not met the burden of establishing by evidence that there was a reason, motivation, suggestion or teaching in the prior art to combine or modify elements of the prior art to obtain the claimed invention. In re O'Farrell, 853 F.2d 894, 902-3, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

None of the cited references teach or suggest that segments of the MAGE-A12 protein are HLA class I binding peptides, particularly Cw*07 binding peptides.

The Examiner states that the motivation to combine the four cited references is that one of ordinary skill in the art would have been motivated to screen MAGE-A12 for HLA binding peptides in order to treat melanoma or other cancers expressing the MAGE-1 related protein MAGE-A12. Office Action at page 12. While MAGE-A12 may be related to MAGE-1, it has a different sequence than MAGE-1, and thus one of ordinary skill in the art would not reasonably expect that it would have the same properties as MAGE-1, other than those specifically identified for MAGE-A12 (e.g., tumor and testis specific expression).

The existence of references that teach that it is possible to identify HLA class II binding motifs do not provide motivation to examine a specific sequence for HLA binding peptides. In

particular, such references (e.g., the US patents cited by the Examiner) do not teach or suggest the specific combinations of sequence and HLA allele that are claimed in the instant application. Claim 1 is directed to specific portions of MAGE-A12. Claim 4 is directed to fragments of MAGE-A12 that bind a specific HLA molecule, the Cw*07 allele. None of the references provide the motivation to examine these particular combinations of peptide and HLA.

Thus the Examiner has not supplied any motivation or reason why one of ordinary skill in the art would select MAGE-A12, from among all of the potential antigenic polypeptide targets, for an analysis of potential HLA class I binding peptides. In essence, the Examiner is suggesting that the claimed invention was obvious to try based on the prior art. "Obvious to try," however, is not a proper and legitimate standard for unpatentability, and does not constitute obviousness. In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988).

Further, because the Examiner did not analyze the level of skill of a person of ordinary skill in the art, the Examiner has not established that one of ordinary skill in the art would have had a reasonable expectation of success in combining or modifying elements of the prior art to obtain the claimed invention, an essential inquiry in any obviousness analysis. In re O'Farrell, 853 F.2d at 902-3, 7 USPQ2d at 1681; Smiths Industries Medical Systems, Inc. v. Vital Signs, Inc., 183 F.3d 1347, 1356, 51 USPQ2d 1415, 1420-21 (Fed. Cir. 1999).

Without the teaching of Applicants' specification that MAGE-A12 does contain HLA class I binding peptides, one of ordinary skill in the art would not have a reasonable expectation of success, particularly with respect to the particular sequences claimed in claims 1-3, and the particular HLA molecule specified in claim 4.

Accordingly, in view of the elements missing from the cited prior art, the lack of motivation to combine the cited prior art references, the impropriety of an "obvious to try" approach, and the lack of a reasonable expectation of success, Applicants respectfully request that the Examiner withdraw the rejection of the claims as unpatentable under 35 U.S.C. 103(a).

In view of the amendments and the arguments presented above, Applicants respectfully request that the rejections of the claims be withdrawn. If the Examiner wishes to expedite the

prosecution of this application in any way, then the Examiner is invited to contact the Applicants' representative at the telephone number listed below.

Respectfully submitted,

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Amended Claims

1.(amended) An isolated MAGE-A12 HLA class I-binding peptide comprising the amino acid sequence of SEQ ID NO:6, or a functional variant thereof which binds a HLA class I molecule[s] comprising one [or more] amino acid addition[s], substitutions[s] or deletion[s].

2.(amended) The isolated MAGE-A12 HLA class I-binding peptide of claim 1 wherein the isolated peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:5, fragments thereof comprising SEQ ID NO:6, and functional variants thereof comprising one amino acid addition, substitution or deletion.

3.(amended) The isolated MAGE-A12 HLA class I-binding peptide of claim 1 wherein the isolated peptide consists of an amino acid sequence selected from the group consisting of SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, fragments thereof comprising SEQ ID NO:6, and functional variants thereof comprising one amino acid addition, substitution or deletion.

4.(amended) An isolated MAGE-A12 HLA class I binding peptide comprising a fragment of the amino acid sequence of SEQ ID NO:2 which binds HLA Cw*07, or a functional variant thereof comprising one [or more] amino acid addition[s], substitution[s] or deletion[s], wherein the functional variant binds HLA Cw*07.